1987. This compound has a very strong affinity for H_1 receptors and a half-life of several days, which accounts for its long duration of activity. This effect permits once-a-day dosing, but it may result in the prolonged inhibition of immediate hypersensitivity skin test reactions. The drug has been effective in treating chronic urticaria and allergic rhinitis. A somewhat slow onset of activity in some patients may be overcome by giving a loading dose of 20 to 30 mg a day for the initial one to three days of therapy.

Mequitazine is a nonsedating antihistamine that has a somewhat narrow therapeutic-to-sedation range. It, too, has a slower onset of activity than terfenadine, but it has been used successfully in Europe for controlling allergic symptoms. Recent studies indicate not only that it is an antagonist of histamine but that it also has the capacity to inhibit mediator release. There are currently no ongoing clinical trials in the United States, so its availability in this country is uncertain.

Most clinical studies with the new nonsedating antihistamines have shown them to be as effective as classic antihistamines in controlling the symptoms of allergic rhinitis. Not all patients respond, however, or respond equally. Furthermore, it appears that some patients whose symptoms are adequately controlled during periods of moderate antigen exposure derive less benefit during peak periods of antigen concentration. Some of these compounds have a longer duration of action, which has raised the question of cumulative effects with prolonged use. There is currently no evidence of this in standard patient care, but the possibility may exist in cases of drug overdose.

At least five other nonsedating antihistamines are under development in the United States. Some of these can be administered once a day, others will be available in a liquid formulation for children and some will be combined with a systemic decongestant such as pseudoephedrine.

The advent of these newer nonsedating antihistamines will offer physicians a wider choice of medication to inhibit the adverse effects of histamine in their allergic patients. Because antihistamines only block the effect of histamine, however, for some patients greater relief of symptoms awaits the development of medications that can prevent or modify the release of, or the effects of, the other mediators of the allergic response. Nevertheless, this new class of nonsedating antihistamines allows the almost 50% of all allergy patients who report sedation from classical antihistamines the opportunity to obtain relief without significant side effects.

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REFERENCES

Kemp JP, Buckley CE, Gershwin ME, et al: Multicenter, double-blind, placebo-controlled trial of terfenadine in seasonal allergic rhinitis and conjunctivitis. Ann Allergy 1985 Jun; 54:502-509

Trzeciakowski JP, Levi R: Antihistamines, *In* Middleton E Jr, Reed CE, Ellis EF (Eds): Allergy: Principles and Practice, 2nd Ed. St Louis, CV Mosby, 1983, pp 575-592

Neuropeptides

THE MECHANISMS by which functionally distinct cells communicate and in the process regulate their physiologic capacities is one of the most active areas of experimentation in modern biology. Early investigations showed that neuropeptides, hormones and lymphokines mediated diverse intercellular modulatory functions in separate systems such as the central nervous, endocrine and immune systems, respectively. It is now clear, however, that bidirectional communication between each of these three systems occurs, and, in the case of neuroimmune interactions, lymphokines such as interleukin 1 and 2 may activate glial cells and astrocytes, whereas neuropeptides have now been shown to modulate immediate hypersensitivity and cell-mediated immune responses.

Neuropeptides released from peripheral sensory nerves including substance P, vasoactive intestinal peptide and somatostatin are potent mediators of smooth muscle and vascular functions. Substance P has been observed to contract intestinal smooth muscle, produce the vasodilation of systemic arterioles and increase the secretion of glycoprotein-rich fluid from human tracheal epithelium, whereas the vasoactive intestinal peptide causes intestinal smooth muscle relaxation and increased vasodilation of cutaneous microvessels. These effects may contribute to the plasma extravasation and alterations in blood flow that accompany inflammatory responses.

The modulation of immediate hypersensitivity reactions by neuropeptides is suggested by the elevated local tissue concentrations of peptides such as substance P and somatostatin detected during acute responses. In vitro studies have shown that substance P acts selectively on mast cells, but not basophils, by an IgE-independent mechanism to cause the release of histamine, leukotrienes and other mediators. In contrast, somatostatin expresses only minimal mast cell-activating activity and may modulate hypersensitivity reactions by indirect mechanisms by inhibiting the release of mediators from immunologically activated basophils.

An understanding of the mechanisms by which neuropeptides alter cell-mediated immune responses has been derived principally from in vitro experimentation. Peptides such as somatostatin and vasoactive intestinal peptide show mainly inhibitory effects on T- and B-lymphocyte activities such as proliferation and immunoglobulin synthesis, respectively. These responses are thought to be mediated by the elevation of intracellular 3′:5′-cyclic adenosine monophosphate levels in response to the neuropeptides binding to specific cell-surface receptors. In contrast, substance P has been shown to exert a stimulatory influence on T-lymphocyte proliferation and to increase the production of IgA from gut-derived lymphocytes. Experiments suggest that these substance P effects are also receptor mediated and are a result of substance P-induced activation of the phosphatidylinositol pathway in a distinct subset of lymphocytes.

The concept of the possible participation of neuropeptides in the pathogenesis of certain disease states has come largely from their chemical or immunochemical detection in tissue extracts or fluids, or by showing that locally administered neuropeptides mimic the features of hypersensitivity. Substance P has been detected in the nasal secretions of humans with allergic rhinitis and in the tissues of patients with urticaria. Its role in these conditions, however, and in other disease states where its immunopathologic role has been suggested, such as in arthritis and asthma, has yet to be conclusively determined. Progress in our understanding of how neuropeptides modulate neuronal and nonneuronal homeo-

static responses will be largely determined by the identification and purification of specific neuropeptide receptors, the in situ analysis of receptor and receptor-gene regulation and the design of novel pharmacologic agonists and antagonists based on our understanding of receptor stereospecificity.

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REFERENCES

Barnes DM: Nervous and immune system disorders linked in a variety of diseases. Science 1986 Apr; 232:160-161

Goetzl EJ (Ed): Proceedings of a conference on neuromodulation of immunity and hypersensitivity. J Immunol 1985; 135(suppl):739S-863S

Iversen LL: The possible role of neuropeptides in the pathophysiology of rheumatoid arthritis (Editorial). J Rheumatol 1985; 12:399-400

Payan DG, McGillis JP, Goetzl EJ: Neuroimmunology. Adv Immunol 1986; 39:299-323

Compliance in Taking Medications

MEDICAL COMPLIANCE has become a major factor in treating chronic disease. It is estimated that 50% of patients do not comply with their medical regimens. Noncompliance is especially a problem in treating patients with allergic disorders, as they frequently must take medication even when they are feeling well.

Compliance will vary in direct proportion to patients' understanding of a medical problem, their perceived benefit of a therapeutic plan, the possibility of medication side effects, the inconvenience of a therapeutic regimen and its cost.

To decrease the incidence of side effects, a new medication regimen should be initiated with the lowest dose possible, then the dosage titrated slowly up to the optimal therapeutic range (unless side effects occur). Potential side effects should be explained to patients. A written sheet, such as the American Medical Association's patient medication instructions or one designed by the physician, should be given to the patient.

It is important for physicians to explain simply why patients must take their medication in a specific manner. This explanation should be given in lay terms, and patients should be provided with clearly written instructions, including the name of the medication, its dosage and schedule.

A practical way to provide these written instructions is through the use of an inexpensive wallet-sized card called the Medical Management Card. This card has been used with success for years at the allergy clinic of the University of California, Irvine. Complimentary copies of the Medical Management Card can be obtained from Mark Havel, Tri-City Medical Center, 4002 Vista Way, Oceanside, CA 92056 or local Key Pharmaceutical representatives.

In addition to the above, using a simplified drug regimen that, where possible, emphasizes the use of once-a-day or twice-a-day medication will greatly increase the probability that a patient will use the medication regularly. Prescribing Uniphyl, a once-a-day theophylline compound, can facilitate compliance and will still be as efficacious as the standard twice-a-day theophylline preparation, Theo-Dur. Theophylline compliance can be monitored by using Acculevel assay, which gives results in 30 minutes.

A simplified drug regimen is especially important in the school-aged population, where medication is frequently missed if a dose has to be taken at school. In younger children (who are often unable to swallow a tablet), it is frequently difficult to administer a liquid preparation because of taste, problems with spillage and problems with dosing. Therefore, the use of a beaded capsule sprinkled over applesauce or other foods is frequently more convenient.

Physicians should be aware of the economics of a therapeutic plan, but not use generic substitutes to save costs if those products will not have the same therapeutic efficacy as the brand-name medication. This may be especially the case for certain long-acting, sustained-release theophylline preparations.

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REFERENCES

Eraker SA, Kirscht JP, Becker MH: Understanding and improving patient compliance. Ann Intern Med 1984 Feb; 100:258-268

Fairshter RD, Bhola R, Thomas R, et al: Comparison of clinical effects and pharmacokinetics of once-daily Uniphyl and twice-daily Theo-Dur in asthmatic patients. Am J Med 1985 Dec 20; 79(suppl SA):48-53

Klein GL, Ziering RW: Improving drug administration in young children with asthma and allergic rhinitis. Immunol Allerg Pract 1983; 5:49-53

Ruffalo RL, Garabedian-Ruffalo SM, Pawlson LG: Patient compliance. Am Fam Pract 1985 Jan, pp 93-100

Vaughan LM, Weinberg MM, Milavetz G, et al: Multicentre evaluation of disposable visual measuring device to assay theophylline from capillary sample. Lancet 1986; 1:184-186

Indications for Giving Immune Globulin Intravenously

THE CURRENT AVAILABILITY of safe intravenous immune globulin preparations has led to applications in various clinical situations. Intramuscular preparations have been used for decades for replacement therapy in antibody deficiency states, but only relatively small doses are tolerated. There is a delay in absorption from the injection site, and some proteolytic degradation may occur before the immunoglobulin is absorbed into the bloodstream. These problems do not exist with intravenously administered immune globulin.

Immune globulin therapy is indicated in patients with humoral immune defects who are unable to produce adequate amounts of IgG (serum IgG levels less than 400 mg per dl in older children and adults or a proved subclass deficiency). Immune globulin given intravenously is preferable to intramuscular preparations in patients with limited muscle mass or bleeding tendencies, those needing large, rapid increases in their serum IgG level or those in whom intramuscular therapy is poorly tolerated. Doses should be individually tailored to a patient's clinical response because susceptibility to infection does not always correlate with IgG serum levels. Generally, levels within one standard deviation of normal for a patient's age can be attained with 150 to 300 mg per kg body weight of immune globulin given intravenously every three weeks, depending on a patient's rate of catabolizing the immune globulin. Deficiency of one or more IgG subclasses in a patient with severe or recurrent infections can be successfully treated with intravenous administration of immune globulin provided the preparation contains adequate concentrations of the deficient subclass(es). Preparations with an IgG subclass distribution similar to that in normal human serum are preferable and are currently available in the United States from Cutter, Hyland and Sandoz laboratories. Prophylaxis or therapy with intravenous immune globulin may also be indicated when